Waugh J, Najafi J, Hawkins L, Hill SL, Eddleston M, Vale JA, Thompson JP, Thomas SHL. Epidemiology and clinical features of toxicity following recreational use of synthetic cannabinoid receptor agonists: a report from the United Kingdom National Poisons Information Service. *Clinical Toxicology* 2016, 54(6), 512-518.

Epidemiology and clinical features of toxicity following recreational use of synthetic cannabinoid receptor agonists. A report from the United Kingdom National Poisons Information Service.

Jennifer Waugh[1], Javad Najafi[2], Leonard Hawkins[2], Simon L Hill[1,2], Michael Eddleston, [3] J Allister Vale, [4] John P Thompson, [5] Simon HL Thomas[1,2]

(UK English version)

[1] Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, NE2 4HH

[2] National Poisons Information Service (Newcastle Unit), Regional Drug and Therapeutics Centre, Newcastle, UK

[3] National Poisons Information Service (Edinburgh Unit), Royal Infirmary of Edinburgh, Edinburgh, UK

[4] National Poisons Information Service (Birmingham Unit), City Hospital, Birmingham, UK

[5] National Poisons Information Service (Cardiff Unit), University Hospital Llandough, Cardiff, UK

Corresponding author

Dr J. Najafi

National Poisons Information Service (Newcastle Unit)

Regional Drug and Therapeutics Centre

16/17 Framlington Place, Newcastle NE2 4AB, United Kingdom

Tel 44 191 282 4642

e-mail: mojtahed@hotmail.com

Keywords: Synthetic cannabinoid receptor agonists (SCRA), clinical features, poisons centres

Abstract

Context. Toxicity from use of synthetic cannabinoid receptor agonists (SCRAs) has been encountered increasingly frequently in many countries.

Objective*.* To characterise presentation rates, demographic profiles and reported clinical features for users of SCRAs referred by health professionals in the United Kingdom to the National Poisons Information Service (NPIS), to compare reported toxicity between commonly used branded products, and to examine the impact of legal control measures on enquiry numbers.

Methods. NPIS telephone enquiry records were searched for SCRA-related terms for the 8 year period 1st January 2007 to 31st December 2014, consolidating multiple enquiries about the same case into a single record. Demographic data, reported exposure details, clinical features and poisoning severity were analysed, excluding cases where SCRA exposure was unlikely.

Results. Enquiries to the NPIS were made concerning 510 individuals relating to probable SCRA use, with annual numbers increasing year on year. Most patients were male (80.8%) and <25 years old (65.1%). Common clinical features reported in the 433 (84.9%) patients reporting SCRA use without other substances included tachycardia (n = 73, 16.9%), reduced level of consciousness (n = 70, 16.2%), agitation or aggression (n = 45, 10.4%), vomiting (n = 30, 6.9%), dizziness (n = 26, 6.0%), confusion (n= 21, 4.8%), mydriasis (n = 20, 4.6%) and hallucinations (n = 20, 4.6%). The Maximum Poisoning Severity Score (PSS) indicated severe toxicity in 36 cases (8.3%). Legal control of 'second generation' SCRAs did not affect the rate of growth in enquiry numbers or the proportion with severe toxicity. The three most commonly reported products were 'Black Mamba' (n= 88, 20.3%), 'Pandora's Box' (n= 65, 15%) and 'Clockwork Orange' (n= 27, 6.2%). Neurological and general features were recorded more often with 'Clockwork Orange' than for 'Black Mamba' and 'Pandora's Box',

but moderate or severe toxicity was significantly less common after reported use of this product.

Conclusions. Enquiries about SCRA-related toxicity have become increasingly frequent in the UK in spite of legal controls and commonly involve younger males. Differences in the patterns of toxicity associated with different branded preparations may occur, although further work with larger patient numbers is needed to confirm this.

Introduction

Synthetic cannabinoid receptor agonists (SCRAs) are increasingly encountered as alternatives to cannabis. [1, 2] They are incorporated into many branded products currently available for purchase from 'head-shops' or via the internet. [1] These usually consist of plant based material to which SCRAs are added. [1, 3]

SCRAs are synthetic modifications to Δ^9-tetrahydrocannabinol (Δ^9-THC), the principal phytocannabinoid occurring in the cannabis plant (Figure 1). [4, 5] Like Δ^9-THC, they are cannabinoid receptor agonists [6] and have similar pharmacological effects. [7, 8] However, unlike the partial agonist Δ^9-THC [1], several SCRAs, such as HU-210 and UR-144, are full cannabinoid receptor agonists [9, 10] and many exhibit an increased binding affinity for both cannabinoid receptors (CB_1 and CB_2) compared to Δ^9-THC. [4, 5, 7, 11, 12] This may explain in part the altered pattern of clinical features and increased severity of toxic effects reported after SCRA use such as encephalopathy and seizure, [13] myocardial infarction, [14] acute kidney injury [15] and extreme psychiatric effects. [16] Some SCRAs are also weak monoamine oxidase inhibitors, which may explain apparent serotoninergic effects. [17] Batch to batch and within product variability in SCRA content [18, 19] and the presence of more than one SCRA in some products [20] may also contribute to unpredictable toxic effects.

There is evidence of a significant increase in the number of SCRA users and associated adverse health effects in recent years. [21, 22, 23] The number of calls to poisons centres in the United States (US) indicates a 229% increase in 2015 compared to 2014. [21] Legal measures to control their use have been taken in many countries. In the United Kingdom (UK), early so-called 'first generation' SCRAs, including JWH-018, were controlled in December 2009 [24] and further legislation to control so-called 'second generation' products, including AM2201 and UR-144, was enacted in February 2013. [25] However, subsequent manipulation of the chemical structure of these compounds has resulted in a further ('third') generation of SCRAs that are not currently legally controlled in the UK including PB-22, 5F-PB-22, STS-135 and 5F-AKB-48. [26] Further legislation is planned, but this will be based on a revised generic description rather than chemical structure. [26]

While there is some published evidence of the increasing use and toxicity of SCRAs, limited evidence has been published examining the impacts of legal controls on presentations with toxicity or comparing toxicity between individual SCRAs and SCRA products. This study was therefore performed to characterise the patterns of referrals with SCRA-related toxicity to the UK poisons centres, describe the features of toxicity encountered, compare reported clinical features and severity of poisoning between the most commonly used products and examine the impact of legal control measures on enquiry numbers.

Methods

The study used fully anonymised data collected routinely during telephone enquiries to the National Poison Information Service (NPIS). In the UK, use of such data does not require ethical approval. The NPIS, commissioned by the Health Protection Agency until April 2013 and then by Public Health England, provides clinical advice to health professionals across the UK about the management of toxicity, including toxic effects from legal and illegal recreational drugs. The service is provided by four units located in Newcastle, Edinburgh, Cardiff and Birmingham that work together to provide an integrated 24 hour service. Health

professionals can access poisons information on-line via the NPIS's TOXBASE website. Additional telephone advice can be provided by specialists in poisons information who are supported by a consultant clinical toxicologist as required for complex and severe cases.

For this study a list of 378 possible search terms was compiled to capture the names of SCRAs and SCRA-containing products. This was done by searching for product terms associated with SCRAs in the academic literature and the internet including websites provided for drug users and by internet drug suppliers. We also used the website of the Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS) project, [27] which was launched in September 2013 and provides details of the analytical content of products sent by drug users from across the UK.

Individual SCRAs were described by generation according to how they were affected by UK drugs legislation, with first generation products being those controlled in December 2009, second generation products those additional SCRAs controlled in February 2013 and third generation products those remaining uncontrolled after that date. Note that classification by generation may vary between countries because of international differences in the timing and detail of drug control measures.

All telephone enquiries containing a reference to any of the search terms at any point in the clinical record were extracted for the 8 year period 1st January 2007 to 31st December 2014. These were then reviewed manually and those with no clear evidence of SCRA use were excluded. For the remaining records, multiple enquiries about the same case were consolidated into a single record, from which the details extracted included the source and date of the enquiry, the age and sex of the patient, the reported exposure substance and route, the recorded clinical features and available laboratory results. For each case the maximum Poisoning Severity Score (PSS), as developed by the World Health Organisation, International Programme on Chemical Safety, Commission of European Union and European Association of Poison Centres and Clinical Toxicologists [28] was also obtained, if

recorded. This validated scale grades the severity of poisoning from 0 (No symptoms or signs related to poisoning) to 4 (death as a result of poisoning).

To minimise the effects of other recreational or pharmaceutical agents on clinical features and severity of toxicity of SCRA, patients who reported using other agents simultaneously were identified (co-use group) and excluded from analyses of clinical features and poisoning severity.

Chi-square tests were used to compare the severity of poisoning among the most commonly used products. The severity of poisoning with SCRA products overall was also compared before and after the second (February 2013) modification of the Misuse of Drug Act.

Results

The search terms that might indicate SCRA exposure generated 1196 entries. After removal of those where SCRA exposure was unlikely and consolidation of multiple enquiries about the same case into a single record, 510 cases of probable SCRA use were identified during the study period, with hospitals (391, 76.7%) and paramedics (63, 12.3%) the most common source of enquiries. Other sources of enquiries included general practitioners (GPs), staff of National Health Service (NHS) patient helplines (NHS 111, NHS 24 or NHS Direct) and the Police. There were very few cases reported prior to 2011, but enquiries increased rapidly between 2011 and 2014 (Figure 2). Isolated SCRA use was reported in most cases (464, 91.0%), but in 46 (9.0 %) there was co-use with other substances, most commonly Central Nervous System (CNS) depressants such as ethanol, opioids or benzodiazepines.

For the 494 enquiries where the gender was known, 399 (80.8%) were male. The median age of SCRA users was 21 years (range 12-78 years, interquartile range 16-29 years). Excluding 24 cases where the age was not documented, 306 (65.1%) were below the age of

25 and 173 (36.8%) below the age of 18 years. Three 12 year old males were the youngest SCRA users reported to the NPIS. (Figure 3)

A maximum PSS was recorded in 479 (93.9%) referrals (Table 1); in the 433 SCRA users without substance co-use who had a maximum PSS recorded, this was 0 (no toxicity) in 37 (8.5%), 1 (minor) in 234 (54.0%), 2 (moderate) in 126 (29.1%) and 3 (severe) in 36 cases (8.3%). There was one reported fatal case resulting from head trauma after a fall, although there was inadequate information to conclude that SCRA toxicity was the direct cause of death. Although the co-use group was excluded from this analysis, there was no significant difference in maximum PSS between those using SCRAs with and without other substances ($p > 0.05$). The most common clinical features reported in these SCRA users without substance co-use were tachycardia, reduced level of consciousness, agitation or aggression, vomiting, dizziness, confusion, mydriasis and hallucinations (Table 2).

There were inadequate numbers of enquiries before and soon after the December 2009 modification to the Misuse of Drugs Act that controlled first generation SCRAs to assess the impact of this. Total enquiry numbers continued to increase in spite of the control of second generation SCRAs in February 2013. (Figure 2) and there was no significant difference in the severity of toxicity between those presenting before and after this date ($p > 0.05$).

Most reported SCRA use involved the use of branded products. The five most commonly reported, with or without co-use of other substances, were ‘Black Mamba’ (n=107, 21.0%) ‘Pandora’s Box’ (n=73, 14.3%), ‘Clockwork Orange’ (n=34, 6.7%), ‘Cherry Bomb’ (n=27, 5.3%) and ‘Annihilation’ (n=19, 3.7%). Enquiries involving ‘Annihilation’ were largely confined to the period before control of second generation SCRAs, while those associated with ‘Pandora’s Box’, ‘Clockwork Orange’ and ‘Cherry Bomb’ emerged subsequently. For ‘Black Mamba’, there was a reduction in telephone enquiries around the time of 2nd generation SCRA control but a subsequent growth in enquiry numbers to a second peak in the 1st quarter of 2014 (Figure 4).

Poisoning severity scores were compared for isolated use of the three most common SCRA products (Table 4). No significant differences were observed comparing ‘Black Mamba’ with ‘Pandora’s Box’ ($p > 0.05$). ‘Clockwork Orange’ was associated with significantly lower poisons severity scores ($p = 0.01$) compared to ‘Pandora’s Box’, but the total numbers of enquiries were small. A higher proportion of cases involving neurological or general features in ‘Clockwork Orange’ users compared to ‘Pandora’s Box’ or ‘Black Mamba’ was observed.

Discussion

These data demonstrate a substantial recent increase in poisons centre enquiries related to SCRA use in the UK, especially between early 2011 and late 2013. These predominantly involve young males, as previously reported in other countries. [30] It is a particular concern that over a third of enquiries involved people less than 18 years of age.

The most common reported clinical features in SCRA users who did not report concurrent use of other substances were tachycardia, reduced level of consciousness, agitation or aggression, vomiting and dizziness. Confusion, hallucinations, chest pain, blood pressure disturbances, and seizures were also reported. These clinical features are consistent with reports from other international studies, [29-34] although several were less commonly documented in this UK case series; this may arise from incomplete reporting of clinical details in NPIS enquiries. While cannabis toxicity presenting to emergency departments was associated with agitation or aggression (23%), psychosis (20%), anxiety (20%) or vomiting (17%) in one case series, [35] several clinical features associated with SCRA use are not typical of cannabis exposure, including bradycardia and seizures. Consistent with earlier reports, [15, 34, 36] renal impairment, as evidenced by elevated plasma creatinine, was also observed in a small proportion of cases.

During the data collection period for this study there were two modifications made to the Misuse of Drugs Act to control SCRAs. The data presented here cannot be used to evaluate first generation control in December 2009 as there were very few NPIS enquiries around the time of that change. However, there was a substantial increase in SCRA use in the second half of 2011 in spite of this earlier legislation. There is no suggestion that second generation control in February 2013 affected the growth in SCRA-related enquiries overall, although these are observational data and the rate of growth in enquiries in the absence of legal control cannot be estimated. Also, the impact of associated publicity on poisons centre enquiries is difficult to estimate, although unlikely to be major for telephone enquiries made by health professionals. Previous research has suggested that first generation control in the UK had a limited impact on internet SCRA sales, with continued supply of SCRAs controlled under the legislation, as well as the emergence of newer uncontrolled compounds. [37] Legislation in the Unites States, Ireland and Australia restricting the sale of SCRAs, however, was associated with reductions in SCRA-related enquiries to poisons centres. [31, 38, 39]

Although total numbers of enquiries continued to increase, there were changes to the patterns of branded SCRA-containing products involved in enquiries (Figure 4). Those relating to 'Annihilation' fell after the introduction of second generation controls. According to Drugwatch, analysis of this product identified the 'second generation' cannabinoids MAM-2201 and UR-144. [40] Enquiries relating to 'Pandora's Box', 'Clockwork Orange' and 'Cherry Bomb' increased after second generation control. Analysis of products submitted to WEDINOS during 2014 has shown these to contain the 3rd generation SCRAs BB-22, 5F-PB-22 and 5F-AKB48. [27] For 'Black Mamba,' the number of cases fell after the time of legal control of second generation SCRAs and none were encountered during the 2nd quarter of 2013. However, this product reappeared in the second half of 2013 and related poison centre enquiries gradually increased after that (Figure 4). Early samples of 'Black Mamba' contained the second generation SCRA AM-2201, [26] but more recent samples

analysed in 2014 by WEDINOS have contained the currently uncontrolled third generation SCRAs 5F-PB-22 and 5F-AKB-48, although there was also one sample containing AM-2201. [27] This suggests that, in response to legal control, suppliers may change the products being sold or the active constituents of popular branded products so that these are no longer affected by the updated legislation.

It is important to consider not only the numbers of enquiries, but also their severity. Legal control could reduce the frequency of severe episodes by reducing availability of substances shown to be associated with acute harms. On the other hand, control of established substances may encourage users to move to newer SCRAs for which there is less experience of use and where toxicity may be greater. We therefore examined the patterns of poisons severity scores by year and also before and after control of second generation products, but found no time-related differences in the proportion of enquiries associated with moderate or severe poisoning (Table 3).

We also compared clinical features and severity of poisoning between the three most commonly encountered SCRA-containing branded products. Samples of all three products commonly contain 5F-PB-22 and 5F-AKB48, [27] but differences in toxicity could arise from differences in dose as there is no quantitative information available on their SCRA content. Exposures to ‘Clockwork Orange’ were associated with a higher proportion of general and neurological features (Table 4), but moderate or severe toxicity was less common with this product. However, the numbers of enquiries for each product, especially ‘Clockwork Orange’, were modest so the reliability of these findings is uncertain and further monitoring is needed.

Use of information collected during poisons centre enquiries has important limitations that need to be taken into account in interpretation. The number of enquiries does not reflect directly the number of clinical exposures or hospital presentations as not all of these will be discussed with a poisons centre. Health professionals may rely on other sources for advice,

including the NPIS poisons information database TOXBASE, restricting telephone enquiries to more severely poisoned or unusual cases. Conversely, several enquiries may be received about the same case and identification and consolidation of duplicated information using anonymised records may not always be possible. Clinical features reported during enquiries are often incomplete because only the data needed to answer the enquiry may be given. Although information on other substances used is sought, accurate information may not be reported by the patient or the enquirer, resulting in an underestimate of the numbers using multiple substances. Also, clinical features that occur after the enquiry has been made are usually not captured. Although follow up is attempted, especially for severe cases, this is often unsuccessful and the final outcome may not be known. This may explain the lower incidence of several clinical features in this series compared with others.

Accurate identification of the chemicals involved in episodes of toxicity is challenging because analytical confirmation is not performed in routine clinical practice. This is a particular problem for SCRAs in view of the large range of branded products involved. The chemical content of these can change with time, [35] therefore comparison using cases of exposure across time to brands that appear similar can be misleading.

Although analysis of clinical features and severity excluded those admitting concurrent use of other substances, the possibility that these may be involved and might have contributed to clinical features in some of these cases cannot be excluded.

Conclusions

NPIS data indicate that cases of toxicity associated with SCRA use have increased in the UK and most commonly involve younger males. Some reported clinical features differ from those associated with cannabis use and severe effects may occur, as previously reported. No clear evidence of an effect of legal control on enquiry numbers or severity was found. Further research is needed to characterise possible differences in toxicity between different branded products.

Declaration of interest

The authors have no declarations of interest to report.

References:

1. Järbe TUC, Gifford RS. Herbal incense: Designer drug blends as cannabimimetics and their assessment by drug discrimination and other in vivo bioassays. Life Sciences 2014;97:64-71.

2. Elsohly MA, Gul W, Wanas AS, Radwan MM. Synthetic cannabinoids: Analysis and metabolites. Life Sciences 2014;97:78-90.

3. United Nations Office on Drug and Crime (UNODC) report. Synthetic Cannabinoids in herbal products. Available at: https://www.unodc.org/documents/scientific/Synthetic_Cannabinoids.pdf. Last accessed: 6th January 2016.

4. Fantegrossi WE, Moran JH, Radominska-Pandya A, Prather PL. Distinct pharmacology and metabolism of K2 synthetic cannabinoids compared to Δ9-THC: Mechanism underlying greater toxicity? Life Sciences 2014;97:45-54.

5. Castaneto MS, Gorelick DA, Desrosiers, NA, Hartman RL, Pirard S, Huestis MA. Synthetic cannabinoids: epidemiology, pharmacodynamics and clinical implications. Drug and Alcohol Dependence 2014;144:12-41.

6. Atwood BK, Lee D, Straiker A, Widlanski TS, Mackie K. CP47,497-C8 and JWH073, commonly found in 'Spice' herbal blends, are potent and efficacious CB(1) cannabinoid receptor agonists. Eur J Pharmacol 2011;659:139-145.

7. Spaderna M, Addy PH, D'Souza DC. Spicing things up: synthetic cannabinoids. Psychopharmacology (Berl) 2013;228:525-540.

8. Monaghan M. Drug Policy Governance in the UK: Lessons from changes to and debates concerning the classification of cannabis under the 1971 Misuse of Drugs Act. International Journal of Drug Policy 2014;25:1025-1030.

9. Fattore L, Fratta W. Beyond THC: the new generation of cannabinoid designer drugs. Frontiers in Behavioral Neuroscience 2011;60:1-12.

10. Gurney SMR, Scott KS, Kacinko KS, Presley BC, Logan BK. Pharmacology, toxicology, and adverse effects of synthetic cannabinoid drugs. Forensic Sci Rev 2014; 26:53-77.

11. Aung MM, Griffin G, Huffman JW, Wu M-J, Keel C, Yang B, Showalter VM, Abood ME, Martin BR. Influence of the N-1 alkyl chain length of cannabimimetic indoles upon CB (1) and CB (2) receptor binding. Drug and Alcohol Dependence 2000;60:133–140.

12. Auwärter V, Dresen S, Weinmann W, Müller M, Pütz M, Ferreirós N . 'Spice' and other herbal blends: harmless incense or cannabinoid designer drugs? J Mass Spectrom 2009;44:832–837.

13. Louh IK, Freeman WD. A 'spicy' encephalopathy: synthetic cannabinoids as cause of encephalopathy and seizure. Critical Care 2014;18:553-554.

14. Mir A, Obafemi A, Young A, Kane C. Myocardial infarction associated with use of the synthetic cannabinoid K2. Pediatrics 2011;128:e1622–e1627.

15. Kazory A, Aiyer R. Synthetic marijuana and acute kidney injury: an unforeseen association. Clin Kidney J 2013;6:330–333.

16. Harris CR, Brown A. Synthetic cannabinoid intoxication: a case series and review. J Emerg Med 2013;44:360–366.

17. Wells DL, Ott CA. The ‘‘new’’ marijuana. Ann Pharmacother 2011; 45(3): 414-417

18. Dunne FJ, Jaffar K, Hashmi S. Legal highs - not so new and still growing in popularity, BJMP 2015; 8(1): a801.

19. Gunderson EW. Synthetic cannabinoids: a new frontier of designer drugs. Ann Inter Med 2013; 159: 563–564.

20. Schneir AB, Baumbacher T. Convulsions associated with the use of a synthetic cannabinoid product. J Med Toxicol 2012;8:62-64.

21. Law R, Schier J, Martin C, Chang A, Wolkin A. Increase in reported adverse health effects related to synthetic cannabinoid use. MMWR 2015;64:618-619.

22. Wood KE. Exposure to bath salts and synthetic tetrahydrocannabinol from 2009 to 2012 in the United States. J Pediatr 2013;163:213-216.

23. National Poisons Information Service Report 2013/2014 Available at: http://www.npis.org/NPISAnnualReport2013-14.pdf. Last accessed: 6th January 2016

24. Advisory Council on the Misuse of Drugs. Consideration of the major cannabinoid agonists (2009). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/119149/acmd-report-agonists.pdf. Last accessed: 6th January 2016

25. Advisory Council of the Misuse of Drugs, Further consideration of the synthetic cannabinoids (2012). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/119042/synthetic-cannabinoids-2012.pdf. Last accessed: 6th January 2016

26. Advisory Council of the Misuse of Drugs. 'Third generation' synthetic Cannabinoids 2014. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/380161/CannabinoidsReport.pdf. Last accessed: 6th January 2016

27. Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS) project. Substance Information. Available at: www.wedinos.org/db/samples. Last accessed: 6th January 2016

28. Persson HE, Sjoberg GK, Haines JA, Pronczuk de Garbino J. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol 1998;36:205-213.

29. Hoyte CO, Jacob J, Monte AA, Al-Jumaan M, Bronstein AC, Heard KJ. A characterization of synthetic cannabinoid exposures reported to the National Poison Data System in 2010; Ann Emerg Med 2012;60:435-438.

30. Forrester M, Kleinschmidt K, Schwarz E, Young A. Synthetic cannabinoid and marijuana exposures reported to poison centers. Hum Exp Toxicol 2012;31:1-6.

31. Brown J, Gunja N, Buckley N. Synthetic cannabinoids: impact of Australian legislation; is the problem Kronic or chronic? Clinical Toxicology 2014;52:364-365.

32. Hermanns-Clausen, M, Kneisel, S, Szabo, B. Auwarter, V. Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings . Addiction 2013;108:534-544.

33. Locatelli CA, Lonati D, Giampreti A, Petrolini V, Vecchio S, Rognoni C, Buscaglia E, Mazzoleni M, Manzo L, Papa P, Valli A. New synthetic cannabinoids intoxications in Italy: Clinical identification and analytical confirmation of cases. European Journal of Emergency Medicine 2011;18:309.

34. Tait RJ, Caldicott D, Mountain D5, Hill SL, Lenton S.A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. Clin Toxicol (Phila). 2016;54:1-13.

35. Dines AM, Wood DM, Galicia M, Yates CM, Heyerdahl F, Hovda KE, Giraudon I, Sedefov R, Dargan PI. Presentations to the emergency department following cannabis use-a multi-centre case series from ten European countries. J Med Toxicol 2015;11: 415-421.

36. Centers for Disease Control and Prevention (CDC). Acute kidney injury associated with synthetic cannabinoid use-multiple States. MMWR 2013;62:93-96.

37. Dargan PI, Hudson S, Ramsey J, Wood DM. The impact of changes in UK classification of the synthetic cannabinoid receptor agonists in 'Spice'. Int J Drug Policy 2011;22:274-277.

38 Wiegand TJ, Marraffa J, Gorodetsky RM, Barton N. Comparison of psychoactive bath salt and synthetic cannabinoid cases pre- and post-federal legislative ban - Evidence of effective control measures in New York State. J Med Toxicol 2013;9:102.

39 Herbert JX, Duggan E, Tracey JA. The effect of legislation on synthetic cannabinoid abuse in Ireland. Clin Toxicol (Phila) 2011;49:240.

40. Drugwatch information sheet (version 1.5). Potent Synthetic Cannabinoid smoking mixtures. Available at: http://www.sdf.org.uk/index.php/download_file/view/671/106/. Last accessed: 6th January 2016

Table 1: Maximum Poisoning Severity Scores (Max PSS) for cases of sole SCRA* use

	Year						
Max PSS n, (%)**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**Total**
None (0)	0	0	0	9 (12.5%)	9 (6.0%)	19 (9.8%)	**37 (8.5%)**
Minor (1)	2 (66.7%)	2 (100%)	4 (33.3%)	39 (54.2%)	88 (58.7%)	99 (51.0%)	**234 (54.0%)**
Moderate (2)	1 (33.3%)	0	5 (41.7%)	19 (26.4%)	40 (26.7%)	61 (31.4%)	**126 (29.1%)**
Severe (3)	0	0	3 (25.0%)	5 (6.9%)	13 (8.7%)	15 (7.7%)	**36 (8.3%)**
Total (Max PSS recorded)	3	2	12	72	150	194	**433**
Max PSS unknown	1	0	0	1	18	11	31
Total	**4**	**2**	**12**	**73**	**168**	**205**	**464**

*Synthetic Cannabinoid Agonist Receptors, **Where known

Table 2: Clinical Features reported to the NPIS* for Synthetic Cannabinoid Receptor Agonist users (in ≥5 reported cases)

Clinical Features	All patients (n=510)		Isolated SCRAs use (n=433)	
	n	%	n	%
General	**33**	**6.5 %**	**28**	**6.5%**
Abnormal Sweating	8	1.6%	7	1.6%
Malaise	10	2.0%	9	2.1%
Other	15	2.9%	11	2.5%
Gastrointestinal	**64**	**12.5%**	**57**	**13.2%**
Vomiting	34	6.7%	30	6.9%
Nausea	16	3.1%	16	3.7%
Abdominal Pain	8	1.6%	7	1.6%
Dry Mouth	6	1.2%	5	1.2%
Neurological	**165**	**32.4%**	**160**	**37.0%**
Reduced level of consciousness	87	17.1%	70	16.2%
Mydriasis	24	4.7%	20	4.6%
Headache	16	3.1%	15	3.5%
Seizure	9	1.8%	7	1.6%
Clonus	6	1.2%	6	1.4%
Cardiorespiratory	**210**	**41.2%**	**191**	**44.1%**
Tachycardia (>100)	81	15.9%	73	16.9%
Dizziness	28	5.5%	26	6.0%
Chest Pain	20	3.9%	20	4.6%
Hypotension (SBP<80)	16	3.1%	15	3.5%
Palpitations	14	2.7%	13	3.0%
Bradycardia (<60)	9	1.8%	8	1.8%
Hypertension (SBP>160)	9	1.8%	7	1.6%
Abnormal ECG	9	1.8%	5	1.2%
Arrhythmia	6	1.2%	6	1.4%
Psychiatric	**121**	**23.7%**	**111**	**25.6%**
Agitation/Aggression	50	9.8%	45	10.4%
Confusion	23	4.5%	21	4.8%
Hallucination	22	4.3%	20	4.6%
Paranoid Ideation/Psychosis	6	1.2%	6	1.4%
Anxiety	6	1.2%	5	1.2%
Speech Disorder	6	1.2%	6	1.4%
Lab Findings	**24**	4.7%	**16**	**3.7%**
Acidosis/Acidosis Lactic	14	2.7%	10	2.3%
Elevated Creatinine	10	2.0%	6	1.4%

* National Poisons Information Service

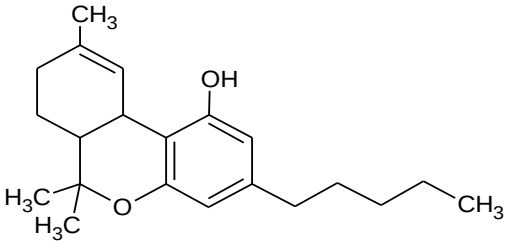
Table 3: Maximum Poisoning Severity Scores for sole SCRA* use before and after implementation of second generation SCRA control in February 2013. No significant difference in the severity of toxicity was found between two groups (P > 0.05).

Maximum PSS n, (%)	**0 (None)**	**1 (Minor)**	**2 (Moderate)**	**3 (Severe)**	**Total**
Jan 2010- Feb 2013	11 (10.9%)	51 (50.5%)	30 (29.7%)	9 (8.9%)	**101**
After Feb 2013	26 (7.9%)	181 (55.0%)	95 (28.9%)	27 (8.2%)	**329**
Total	**37 (8.6%)**	**232 (54.0%)**	**125 (29.1%)**	**36 (8.4%)**	**430**

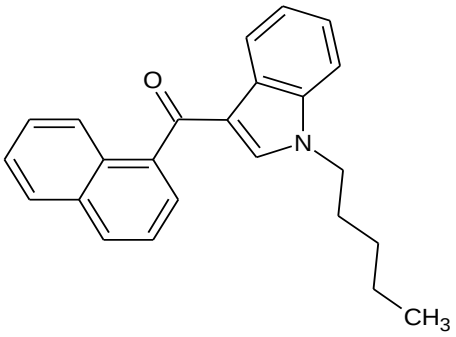
* Synthetic Cannabinoid Receptor Agonist

Table 4: Clinical features and Maximum Poisoning Severity Scores (PSS) for the three most commonly used Synthetic Cannabinoid Receptor Agonist products, without reported co-use of other substances.

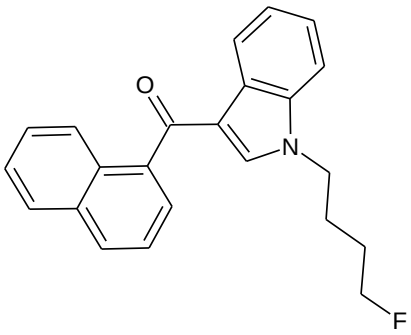
	Black Mamba n=88	**Pandora's Box** n=65	**Clockwork Orange** n=27
Clinical features			
Cardiovascular	36 (40.9%)	28 (43.1%)	12 (44.4%)
Neurological	19 (21.6%)	12 (18.5%)	12 (44.4%)
Psychiatric	25 (28.4%)	17 (26.2%)	8 (29.6%)
Gastrointestinal	7 (8.0%)	9 (13.8%)	2 (7.4%)
General	5 (5.7%)	2 (3.1%)	6 (22.2%)
Lab findings	7 (8.0%)	4 (6.2%)	1 (3.7%)
Maximum PSS			
None (0)	7 (8.0%)	7 (10.8%)	1 (3.7%)
Minor (1)	53 (60.2%)	31 (47.7%)	23 (85.2%)
Moderate (2)	22 (25.0%)	22 (33.8%)	3 (11.1%)
Severe (3)	6 (6.8%)	5 (7.7%)	0 (0%)



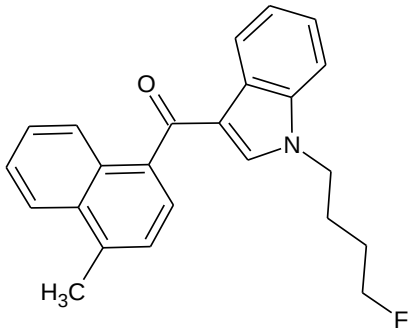
Δ^9- THC



JWH-018



AM-2210



MAM-2210

Figure 1. Chemical structure of Δ^9-Tetrahydrocannabinol (THC) and three examples of synthetic cannabinoid receptor agonists.

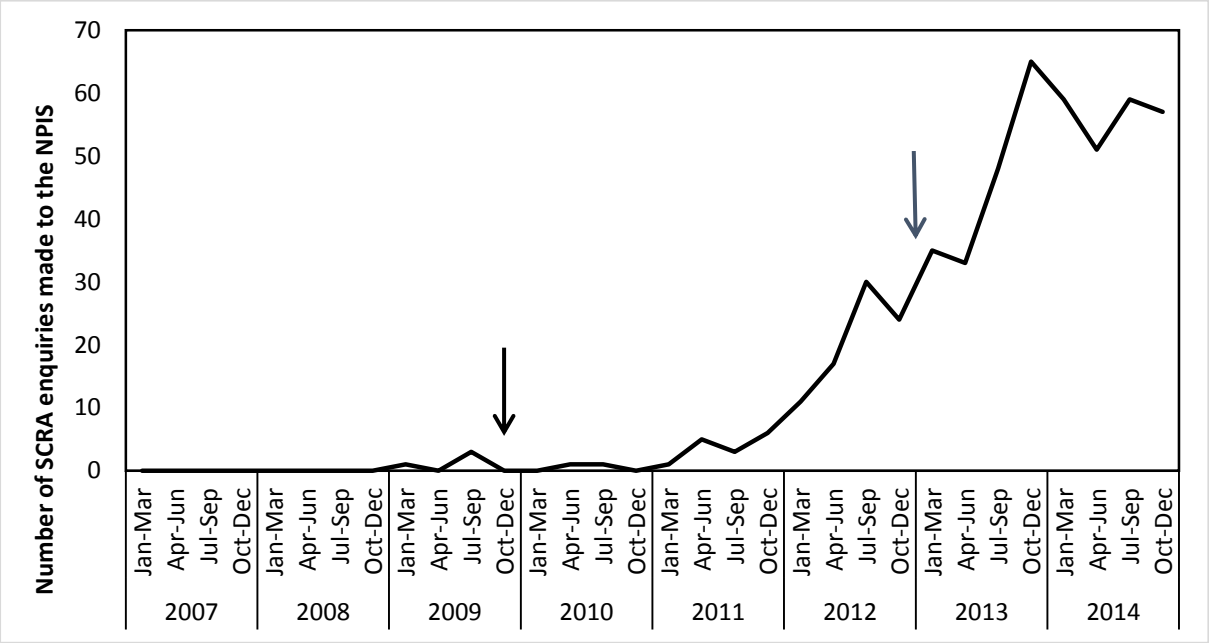


Figure 2: Quarterly numbers of reported cases of synthetic cannabinoid receptor agonist (SCRA) related toxicity referred to the National Poisons Information Service (NPIS) from 2007 to 2014. Arrows indicate the timing of legal control of first and second generation SCRAs (Dec 2009 and Feb 2013).

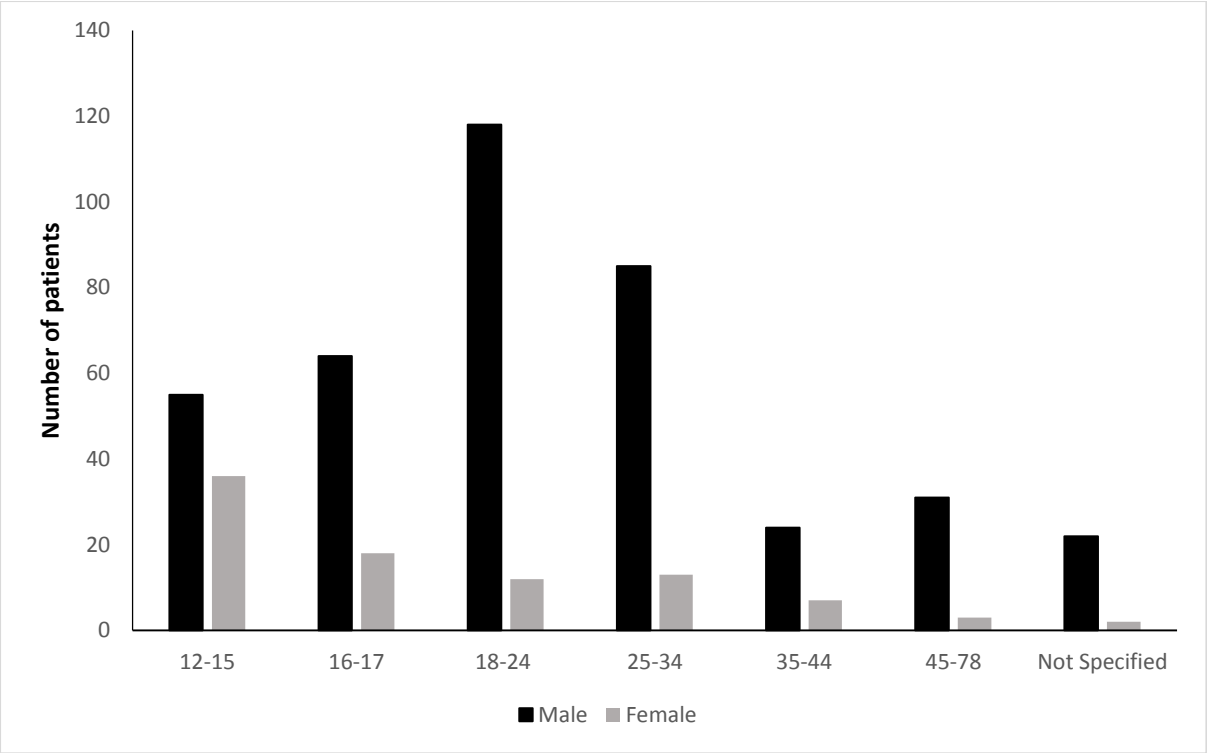


Figure 3: Age (in year) and gender distribution of synthetic cannabinoid receptor agonist users.

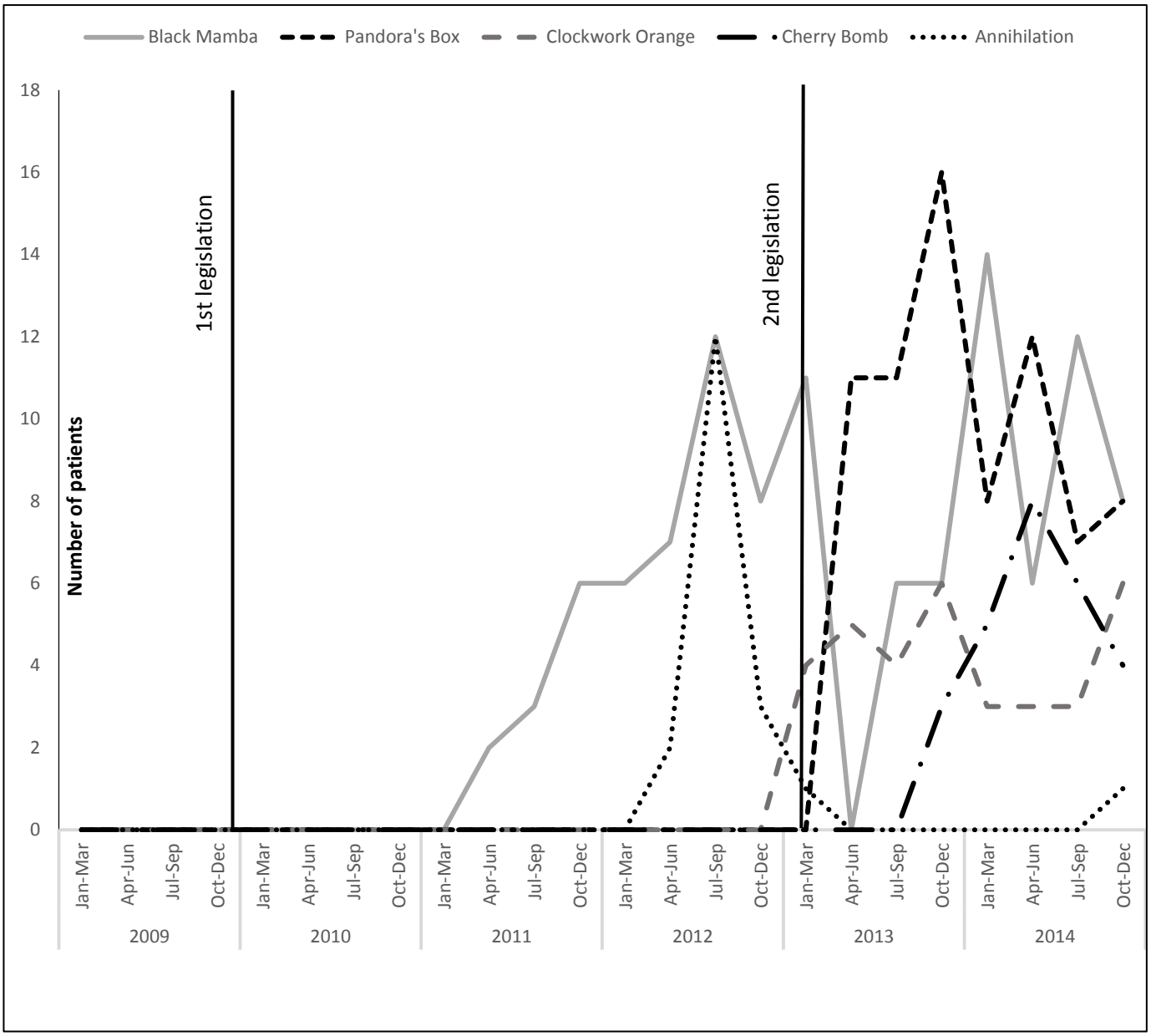


Figure 4: Quarterly numbers of reported cases relating to the 5 synthetic cannabinoid receptor agonist (SCRA) products most commonly reported to the National Poisons Information Service between 2009 and 2014. Arrows indicate the

timing of legal control of first and second generation SCRAs (December 2009 and February 2013).